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(54) **Stabilized pharmaceutical compositions containing angiotensin-converting enzyme inhibitors.**

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EP-A- 0 170 775
FR-A- 2 227 856
US-A- 4 584 299

DICTIONNAIRE VIDAL 1985, Cahier complémentaire, pages 10,11, O.V.P., Paris, FR; "Renitec"

CHEMICAL ABSTRACTS, vol. 101, no. 19, 5th November 1984, page 35, abstract no. 163417j, Columbus, Ohio, US; P.H. VLASSES et al.: "Comparative antihypertensive effects of enalapril maleate and hydrochlorothiazide, alone in combination"

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CHEMICAL ABSTRACTS, vol. 106, no. 6, 9th February 1987, page 352, abstract no. 38377y, Columbus, Ohio, US; P.K. SHIROMANI et al.: "Effect of moisture on the physical and chemical stability of granulations and tablets of the angiotensin converting enzyme inhibitor, enalapril malcate"	

Description

Certain ACE (Angiotensin converting Enzyme) inhibitors, which are useful as antihypertensives, are susceptible to certain types of degradation. Specifically, quinapril and structurally-related drugs can degrade via (1) cyclization via internal nucleophilic attack to form substituted diketopiperazines, (2) hydrolysis of the side-chain ester group, and (3) oxidation to form products having often unwanted coloration.

It has been discovered that stable compositions containing ACE inhibitors of the type discussed above can be produced using alkali or alkaline earth metal carbonates and saccharides as stabilizers.

In one embodiment, 48.6 wt % magnesium carbonate is combined with 5.4 wt % quinapril hydrochloride with the inclusion of 38.0 wt % lactose to yield a composition which withstands oxidative, hydrolytic, and cyclization degradation at 60 ° C for one month.

The Dictionnaire Vidal (1985) Cahier Complémentaire on page 10, left column, describes an enalapril maleate drug named RENITEC, which as excipients contains lactose and monosodium carbonate. This document, however, does not describe the usefulness of a combination of an alkali or alkaline earth metal carbonate and a saccharide for the stabilisation of ACE inhibitors.

The compositions of the invention have several advantages over compositions which do not contain the stabilizing additive(s) discussed herein.

Principally, the active ingredients or drugs contained therein are virtually preserved from cyclization and hydrolysis. In addition, the discoloration which sometimes occurs when ACE inhibitors of this class are formulated and allowed to stand for significant periods of time is minimized or eliminated completely. Thus, a stable tabletted quinapril formulation can be produced which will undergo no detectable oxidative discoloration.

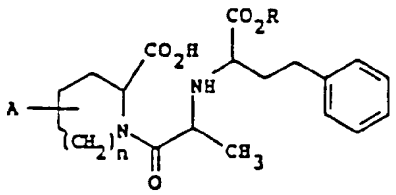
In addition to having greater storage stability, the instant formulations are rendered more suitable for use in drug combinations.

These and other advantages of the invention will become apparent from a consideration of the following description of the invention.

The invention deals with:

I. A pharmaceutical composition which contains:

(a) 1 - 70% of a compound of the formula



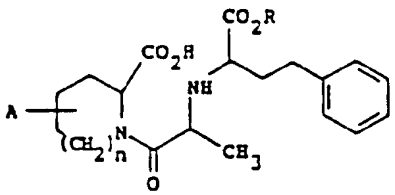
wherein A is absent, a fused five, six, or seven-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by one or two alkoxy groups having one to four carbon atoms; n is zero or one, and R is hydrogen or alkyl having one to five carbon atoms, or a pharmaceutically acceptable acid addition salt thereof,

(b) 1 - 90% of an alkali or alkaline earth metal carbonate and

(c) 5 - 90% of a saccharide

except a composition containing for (a), (b) and (c) enalapril maleate, lactose and monosodium carbonate and with the proviso that the sum of (a), (b) and (c) does not exceed 100%.

II. Use of a composition consisting of 1 - 90% of an alkali or alkaline earth metal carbonate and 5 - 90% of a saccharide to inhibit cyclization, discoloration and hydrolysis in a compound of the formula



wherein A is absent, a fused five, six, or seven-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by one or two alkoxy groups having one to four carbon atoms; n is zero or one, and R is hydrogen or alkyl having one to five carbon atoms, or a pharmaceutically acceptable acid addition salt thereof,

with the proviso that the compound is present in an amount of 1 to 70% and the sum of the above ingredients does not exceed 100%.

III. A process for stabilizing an ACE inhibitor drug as defined in claim 1 against cyclization which comprises the step of contacting the drug with:

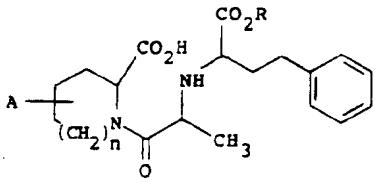
(a) a suitable amount of an alkali or alkaline earth metal salt and,

(b) one or more saccharides.

Preferably, the compositions and processes made and used in accordance with the invention will also contain one or more substances which do not interfere with the function of the stabilizing additive(s). Generally, lubricants, such as hydrogenated vegetable oils and talc, binders, such as gelatin, and/or disintegrants, such as polyplasdone, are suitable.

The compositions of the invention contain at least one ACE inhibitor and, optionally, one or more other medicament drugs or beneficial substances.

The ACE inhibitors being susceptible to cyclization, hydrolysis and/or discoloration are compounds conforming to the general formula



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wherein A is absent, a fused five, six, or seven-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by one or two alkoxy groups having one to four carbon atoms; n is zero or one, and R is hydrogen or alkyl having one to five carbon atoms. Preferably A is absent, a fused five or six-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by two methoxy groups; n is zero or one, and R is hydrogen or ethyl.

Particularly valuable are enalapril, quinapril, or indolapril, their corresponding free acids or pharmaceutically acceptable acid addition or base salts thereof.

Compounds of this type are disclosed in US Patents 4,344,949, 4,374,829, and 4,425,355.

The total drug content of the final composition will be 1 to 70%, preferably from 1% to 25%.

All percentages stated herein are weight percentages based on total composition weight, unless otherwise stated.

The daily dosages of the pharmaceutical preparations of the invention depend upon the nature of the dosage form, the nature of the drug(s) and the type and extent of any interactive(s), in drug combinations. Thus, the therapeutic needs of the individual patient and the desires of the prescribing physician dictate the dosage levels to be employed.

In general, however, the manufacturer's specifications for any drug or drug combination are useful guides to administration. The Physicians Desk Reference or other suitable publication can be consulted to ascertain appropriate dosage levels.

Nonetheless, typical dosage levels for quinapril and enalapril are from about 1 mg to about 80 mg per dosage.

Suitable categories of drugs that may be employed in addition to ACE inhibitors in the instant compositions may vary widely and generally represent any stable drug combination.

Illustrative categories and specific examples include:

(a) Diuretics, such as hydrochlorothiazide.

(b) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride;

(c) Antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate,

(d) Decongestants, such as phenylephedrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine; and

(e) Various alkaloids, such as codeine phosphate, codeine sulfate, and morphine.

(f) Mineral supplements such as potassium chloride and the like.

The medicaments and/or other beneficial substances to be used herein may be selected from a wide variety of substances and pharmaceutically acceptable forms thereof, e.g., their acid addition salts. Both organic and inorganic salts may be used provided the drug maintains its medicament value. Exemplary acid salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinate, citrate, salicylate, sulfate, acetate, and the like. Mixtures are operable.

One preferred group of drugs to be used in combination with ACE inhibitors includes: beta-blockers, diuretics, calcium blockers, and the like.

The cyclization and hydrolytic instability which are exhibited by certain of the drugs discussed above can be overcome via the use of a suitable quantity, i.e., an effective amount of an alkaline stabilizer, together with saccharides.

The alkaline stabilizers of the invention include the inorganic salts of metals of Groups I and II of the Periodic Table. Thus, salts of alkali and alkaline earth metals are operable. Magnesium, calcium, and sodium are preferred. Magnesium is most preferred.

The anionic portion of the salt employee may be any which does not deleteriously affect the stability of the overall formulation. Thus, borates, silicates, and carbonates are contemplated. Carbonates are preferred. Mixtures are operable.

The quantity of the stabilizer component to be used will lie between 1% and 90%, preferably 10% to 80%. In general, any amount which will effectively retard or prevent degradation of the ACE inhibitor component(s) can be used.

The saccharide components to be used in the pharmaceutical products and methods of the invention are substances which are compatible with the alkali or alkaline earth metal-containing stabilizers. Generally, they are substances which do not contain groups which could significantly interfere with the function of either the metal-containing component or the drug component. Mannitol, lactose, and other sugars are preferred. Mixtures are operable.

Generally, the quantity of saccharide present will be from 5% to 90%, preferably 10% to 80%.

The optional excipients which can be used in the instant compositions are also substances which must be compatible with the alkali or alkaline earth metal-containing stabilizers so that it does not interfere with its function in the composition.

The compositions of the invention may contain suitable quantities of disintegrating agents, carriers, diluents, pigments, binders, colorants, lubricants, and other additives conventionally used in the production of pharmaceutical products.

Useful disintegrating agents can be chosen from those generally found suitable in pharmaceutical preparations. Thus, modified starch, polyvinyl pyrrolidone (cross-linked or uncross-linked) and modified cellulose derivatives can be employed. Cross-linked polyvinylpyrrolidone is preferred. Mixtures are operable. The disintegrant component will generally comprise 1% to 15% of the total composition.

Useful lubricants include those generally used in pharmaceutical formulation to assist in the processing of one or more materials during the preparation of a final dosage form. Among the lubricants contemplated for use herein are stearates of magnesium, calcium or zinc, and hydrogenated vegetable oils. Magnesium stearate is a preferred lubricant. Mixtures are operable. The lubricant component will, when present, generally comprise from 0.1 to 5%, preferably 0.5 to 3% of the total composition.

The composition of the invention may also contain from 1 to 10%, preferably 2 to 7% of a binder. Useful binders include gelatin, polyvinylpyrrolidone, and the like. Gelatin is preferred. Mixtures are operable.

Any techniques for processing the products of the invention which are appropriate can be employed. A wet granulation process is preferred.

The percentages in which excipients are used are not critical. In general, their quantities will be consistent with the amount given above for the drug, stabilizer, and lubricant components, i.e., they make up the remainder of the composition.

The final form of the pharmaceutical preparations made in accordance with the invention can vary greatly. Thus, tablets, capsules, sachets, sprinklers, pomades, transdermal compositions, buccal preparations, candy compositions, nasal formulations, ocular compositions, and the like are contemplated. Orally administrable forms, i.e., tablets, caplets, and capsules, are preferred.

Solid, semi-solid, and liquid formulations can be made. However, solids are highly preferred.

The drug preparations can be adapted for immediate, slow, or sustained release profiles, or any combination of these. Thus, a formulation adapted to give an initial loading dosage within 30 minutes followed by sustained release of the remaining drug over 4 to 12 hours is contemplated. Sustained and immediate release formulations are preferred.

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

Example A

The following materials were combined by the wet granulation method for the manufacture of 5 mg tablets.

Quinapril Hydrochloride	5.4 mg
Magnesium Carbonate	46.6 mg
Lactose	38.0 mg
Gelatin	5.0 mg
Polyplasdone (Polyvinylpyrrolidone)	4.0 mg
Magnesium Stearate	1.0 mg

Example B

The following materials were processed by wet granulation for 40 mg tablets.

Quinapril Hydrochloride	43.4 mg
Magnesium Carbonate	250.0 mg
Lactose	66.6 mg
Gelatin	20.0 mg
Polyplasdone (Polyvinylpyrrolidone)	16.0 mg
Magnesium Stearate	40 mg

Example C

The following standard composition was processed for 5 mg tablets without the addition of a stabilizer of the present invention.

Quinapril Hydrochloride	5.425 g
Lactose Anhydrous	119.575 g
Microcrystalline Cellulose	14.775 g
Disodium EDTA	0.225 g
Sterotex HM (hydrogenated vegetable oil)	1.500 g
Syloid 244 (Silica Gel)	3.000 g
Stearic Acid	4.500 g
Ascorbic Acid USP	1.000 g
Water, Purified USP	2.250 g

Example D

The following materials were combined as in Example A for the manufacture of 5-mg tablets.

Quinapril Hydrochloride	5.4 mg
Magnesium Carbonate	88.4 mg
Gelatin	5.2 mg
Magnesium Stearate	1.0 mg

Example E

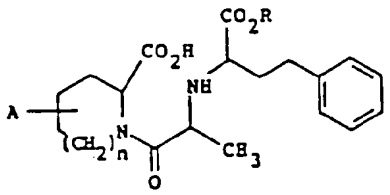
Stability of the tablets prepared in the previous examples were tested at 60 ° C for one month.

	Quinapril(%)[a]	Degradation Products (%)	
		Diketopiperazine	Hydrolysis Product
Example A	97.1	0.7	2.0
Example B	98.1	0.6	1.2
Example C[b]	68.1	32.4	<1
Example D	93.0	0.5	8.0

[a]Percent of original quinapril content.
[b]Analysis was carried out after five days at 60 ° C.

Claims

1. A pharmaceutical composition which contains:
(a) 1 - 70% of a compound of the formula



wherein A is absent, a fused five, six, or seven-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by one or two alkoxy groups having one to four carbon atoms; n is zero or one, and R is hydrogen or alkyl having one to five carbon atoms, or a pharmaceutically acceptable acid addition salt thereof,
(b) 1 - 90% of an alkali or alkaline earth metal carbonate and
(c) 5 - 90% of a saccharide
except a composition containing for (a), (b) and (c) enalapril maleate, lactose and monosodium carbonate and with the proviso that the sum of (a), (b) and (c) does not exceed 100%.

2. The composition of Claim 1 wherein (b) contains magnesium carbonate.

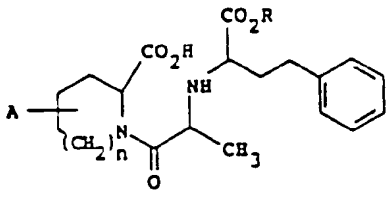
3. The composition of Claim 1 or 2 wherein (c) contains at least one of mannitol and lactose.

4. The composition of Claims 1 to 3 wherein A is absent, a fused five or six-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by two methoxy groups; n is zero or one, and R is hydrogen or ethyl, or a pharmaceutically acceptable acid addition salt thereof.

5. The composition of Claims 1 to 4 wherein (a) is quinapril, indolapril, enalapril, or a pharmaceutically acceptable acid addition salt thereof.

6. The composition of Claims 1 to 5 wherein (a) contains at least one additional drug.

7. Use of a composition consisting of 1 - 90% of an alkali or alkaline earth metal carbonate and 5 - 90% of a saccharide to inhibit cyclization, discoloration and hydrolysis in a compound of the formula

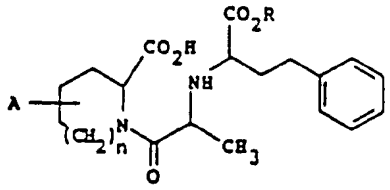


wherein A is absent, a fused five, six, or seven-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by one or two alkoxy groups having one to four carbon atoms; n is zero or one, and R is hydrogen or alkyl having one to five carbon atoms, or a pharmaceutically acceptable acid addition salt thereof,
with the proviso that the compound is present in an amount of 1 to 70% and the sum of the above ingredients does not exceed 100%.

8. Use of a composition of claim 7, wherein the carbonate is magnesium carbonate.

9. Use of a composition of Claim 7 or 8, wherein the saccharide is at least one of mannitol and lactose.

10. Use of a composition of claim 7 to 9 to inhibit cyclization, discoloration and hydrolysis in a compound of the formula



wherein A is absent, a fused five or six-membered cycloaliphatic ring or a fused benzene ring which is unsubstituted or substituted by two methoxy groups; n is zero or one, and R is hydrogen or ethyl, or a pharmaceutically acceptable acid addition salt thereof.

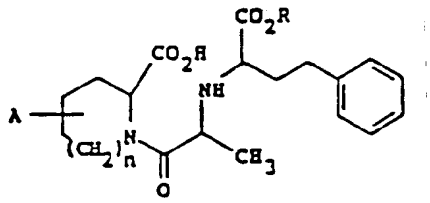
11. Use of a composition of claims 7 to 10 to inhibit cyclization, discoloration and hydrolysis in quinapril, indolapril, enalapril, or a pharmaceutically acceptable acid addition salt thereof.

12. A process for stabilizing an ACE inhibitor drug as defined in claim 1 against cyclization which comprises the step of contacting the drug with:
(a) a suitable amount of an alkali or alkaline earth metal salt and,
(b) one or more saccharides.

13. The process of claim 12, wherein the drug is selected from the group consisting of quinapril, enalapril, and indolapril, or a pharmaceutically acceptable acid addition salt thereof.

Patentansprüche

1. Pharmazeutische Zusammensetzung, welche
(a) 1 - 70 % einer Verbindung der Formel



worin A abwesend, ein kondensierter fünf-, sechs- oder siebengliedriger cycloaliphatischer Ring oder kondensierter Benzolring, welcher unsubstituiert, oder mit ein, zwei oder drei Alkoxygruppen mit ein bis vier Kohlenstoffatomen subsituiert ist, ist, n Null oder eins ist; R Wasserstoff oder Alkyl mit ein bis fünf Kohlenstoffatomen ist oder ein pharmazeutisch verträgliches Säureadditionssalz davon,
(b) 1 - 90 % eines Alkali- oder Erdalkalimetallcarbonates und
(c) 5 - 90 % eines Saccharides, enthält, wobei eine Zusammensetzung, welche für (a), (b) und (c) Enalaprilmaleat, Lactose und Mononatriumcarbonat enthält, ausgenommen ist und mit dem Proviso, daß die Summe von (a), (b) und (c) 100 % nicht übersteigt.

2. Zusammensetzung nach Anspruch 1, worin (b) Magnesiumcarbonat enthält.

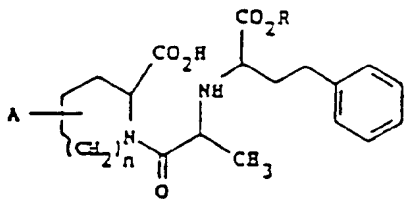
3. Zusammensetzung von Anspruch 1 oder 2, worin (c) wenigstens eine der Substanzen Mannitol oder Lactose enthält.

4. Zusammensetzung nach den Ansprüchen 1 bis 3, worin (a) abwesend, ein kondensierter fünf- oder sechsgliedriger cycloaliphatischer Ring oder kondensierter Benzolring, welcher unsubstituiert oder durch zwei Methoxygruppen substituiert ist, ist, n Null oder eins ist und R Wasserstoff oder Ethyl bedeutet oder ein pharmazeutisch verträgliches Säureadditionssalz davon.

5. Zusammensetzung nach den Ansprüchen 1 bis 4, worin (a) Quinapril, Indolapril, Enalapril bedeutet, oder ein pharmazeutisch verträgliches Säureadditionssalz davon.

6. Zuammensetzung nach den Ansprüchen 1 bis 5, worin (a) wenigstens einen zusätzlichen Wirkstoff enthält.

7. Verwendung einer Zusammensetzung bestehend aus 1 - 90 % eines Alkali- oder Erdalkalimetallcarbonates und 5 - 90 % eines Saccharides, um die Cyklisierung, Verfärbung und Hydrolyse einer Verbindung der Formel



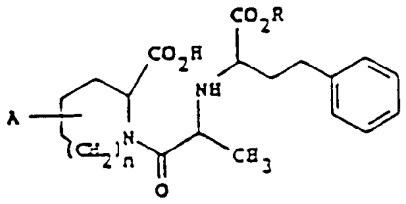
worin A abwesend, ein kondensierter fünf-, sechs- oder siebengliedriger cycloaliphatischer Ring oder kondensierter Benzolring, welcher unsubstituiert oder durch ein oder zwei Alkoxygruppen mit ein bis vier Kohlenstoffatomen substituiert ist, ist, n Null oder eins ist und R Wasserstoff oder Alkyl mit ein bis fünf Kohlenstoffatomen bedeutet, oder ein pharmazeutisch verträglichen Säureadditionssalzes davon ist, zu inhibieren, mit dem Proviso, daß die Verbindung in einer Menge von 1-70 % vorliegt und die Summe der obigen Bestandteile 100 % nicht übersteigt.

8. Verwendung einer Zusammensetzung nach Anspruch 7, worin das Carbonat Magnesiumcarbonat ist.

9. Verwendung einer Zusammensetzung nach einem der Ansprüche 7 oder 8, worin das Saccharid

wenigstens eine Verbindung, gewählt aus Mannitol oder Lactose ist.

10. Verwendung einer Zusammensetzung nach den Ansprüchen 7 bis 9, um die Cyclisierung, Verfärbung und Hydrolyse einer Verbindung der Formel



worin, A abwesend, ein kondensierter fünf- oder sechsgliedriger cycloaliphatischer Ring oder ein kondensierter Benzolring, welcher unsubstituiert oder mit zwei Methoxygruppen substituiert ist, ist, n Null oder eins ist und R Wasserstoff oder Ethyl ist, oder ein pharmazeutisch verträgliches Säureadditionssalz davon bedeutet, zu inhibieren.

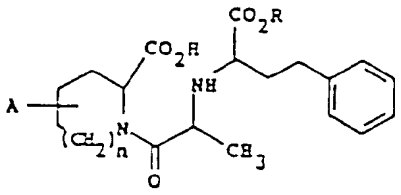
11. Verwendung einer Zusammensetzung nach einem der Ansprüche 7 bis 10, um die Cyclisierung, Verfärbung oder Hydrolyse in Quinapril, Indolapril, Enalapril oder einen pharmazeutisch verträglichen Säuresalz davon, zu inhibieren.

12. Verfahren zum Stabilisieren eines ACE Inhibitorwirkstoffes, welcher wie in Anspruch 1 definiert ist, gegen Cyclisierung, welches Verfahren den Schritt der Kontaktierung des Wirkstoffes mit
(a) einer geeigneten Menge eines Alkali- oder Erdalkalimetallsalzes und
(b) einem oder mehreren Sacchariden umfaßt.

13. Verfahren nach Anspruch 12, worin der Wirkstoff aus der Gruppe bestehend aus Quinapril, Enalapril und Indolapril oder einem pharmazeutisch verträglichen Säureadditionssalz davon gewählt ist.

Revendications

1. Une composition pharmaceutique qui contient:
a) de 1 à 70% d'un composé de formule:



dans laquelle:
A est absent, est un cycle cycloaliphatique accolé contenant 5, 6 ou 7 atomes ou un cycle benzénique accolé qui est non substitué ou substitué par un ou deux groupes alkoxy comprenant de 1 à 4 atomes de carbone,
n est 0 ou 1, et
R est un atome d'hydrogène ou un groupe alkyle ayant de 1 à 5 atomes de carbone,
ou un de leurs sels d'addition d'acide pharmaceutiquement acceptable,
b) de 1 à 90% d'un carbonate de métal alcalin ou alcalino-terreux, et
c) de 5 à 90% d'un saccharide;
à l'exception d'une composition contenant pour (a), (b) et (c) du maléate d'énalapril, du lactose et du carbonate de monosodium, avec la condition que la somme de (a), (b) et (c) n'excède pas 100%.

2. La composition selon la revendication 1, dans laquelle (b) contient du carbonate de magnésium.

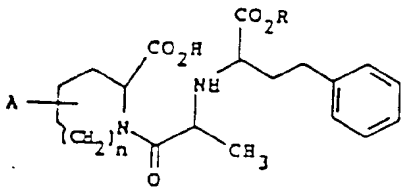
3. La composition selon la revendication 1 ou 2, dans laquelle (c) contient au moins un des composés mannitol et lactose.

4. La composition selon les revendications 1 à 3, dans laquelle:
   - A est absent, est un cycle cycloaliphatique accolé contenant de 5 ou 6 atomes ou un cycle benzénique qui est non substitué ou substitué par deux groupes méthoxy ;
   - n est 0 ou 1; et
   - R est un atome d'hydrogène ou un groupe éthyle, ou un de ses sels d'addition d'acide pharmaceutiquement acceptable.

5. La composition selon les revendications 1 à 4, dans laquelle (a) est: quinapril, indolapril, énalapril ou un de leurs sels d'addition d'acide pharmaceutiquement acceptable.

6. La composition selon les revendications 1 à 5, dans laquelle (a) contient au moins un médicament d'addition.

7. Utilisation d'une composition consistant en 1 à 90% d'un carbonate de métal alcalin ou alcalino-terreux et de 5 à 90% d'un saccharide, afin d'inhiber la cyclisation, la décoloration et l'hydrolyse dans un composé de formule:



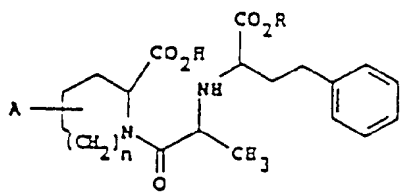
dans laquelle:
- A est absent, est un cycle cycloaliphatique accolé contenant 5, 6 ou 7 atomes ou un cycle benzénique accolé qui est non substitué ou substitué par un ou deux groupes alkoxy comprenant 1 à 4 atomes de carbone,
- n est 0 ou 1, et
- R est un atome d'hydrogène ou un groupe alkyle ayant de 1 à 5 atomes de carbone,

ou un de leurs sels d'addition d'acide pharmaceutiquement acceptable,
avec la condition que le composé soit présent en une quantité comprise entre 1 et 70% et que la somme des ingrédients cités ci-dessus n'excède pas 100%.

8. Utilisation d'une composition selon la revendication 7, dans laquelle le carbonate est le carbonate de magnésium.

9. Utilisation d'une composition selon la revendication 7 ou 8, dans laquelle le saccharide est au moins un des composés consistant en mannitol et lactose.

10. Utilisation d'une composition selon les revendications 7 à 9, pour inhiber la cyclisation, le décoloration et l'hydrolyse d'un composé de formule:



dans laquelle:

A est absent, est un cycle cycloaliphatique accolé contenant 5 ou 6 atomes ou un cycle benzénique qui est non substitué ou substitué par deux groupes méthoxy ;

n est 0 ou 1; et

R est un atome d'hydrogène ou un groupe éthyle,

ou un de ses sels d'addition d'acide pharmaceutiquement acceptable.

11. Utilisation d'une composition selon les revendications 7 à 10, pour inhiber la cyclisation, la décoloration et l'hydrolyse dans la quinapril, l'indolapril, l'énalapril ou un de leurs sels d'addition d'acide pharmaceutiquement acceptable.

12. Un procédé de stabilisation d'un médicament inhibiteur de l'ECA tel que défini dans la revendication 1, contre la cyclisation, qui comprend les étapes de mise en contact du médicament avec:

a) une quantité appropriée d'un sel de métal alcalin ou alcalino-terreux, et

b) un ou plusieurs saccharides.

13. Le procédé selon la revendication 12, dans lequel le médicament est choisi parmi le groupe comprenant la quinapril, l'énalapril et l'indolapril, ou un de leurs sels d'addition d'acide pharmaceutiquement acceptable.